UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/712,819	11/13/2000	Fred J. Stevens	0003/00537	9146

7590 07/29/2002

Cherskov & Flaynik
The Civic Opera Building
20 N Wacker Drive
Chicago, IL 60606

EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	13

DATE MAILED: 07/29/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/712,819	STEVENS ET AL.	
	Examiner	Art Unit	
	" Neon" Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 March 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13 and 15-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13 and 15-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notic to comply sequence rules* .

DETAILED ACTION

1. Claims 1-13 and 15-20 are pending.

2. Applicant's election without traverse of Group I claims 1-13 and 15-20 drawn to a method for minimizing the aggregation tendencies for an amyloid forming protein, filed 3/11/02, is acknowledged.

3. Claims 1-13 and 15-20 drawn to a method for minimizing the aggregation tendencies for an amyloid forming protein are being acted upon in this Office Action.

4. This application contains sequence disclosures that are encompassed by the definitions for amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Amino Acid Sequence Disclosures. It is noted that peptides "FTLEISR" and "LTLKLSR" recited in claim 13 were not included in the sequence listing in paper and computer readable form. Please see enclosed Notice to comply with sequence rule.

5. Applicant should amend the first line of the specification to reflect the relationship between the instant application and 60/165,424 filed 11/14/1999 stated on the oath.

6. The drawings, filed 11/13/00, are not approved. Please see enclosed PTO 948, Notice of Draftsperson's Patent Drawing Review. Appropriate action is required.

7. The abstract of the disclosure is objected to because SEQ ID NO is required for Phe_{71}-Thr_{72}-Leu_{73}-Thr_{74}-Ile_{75}-Ser_{76}-Ser_{77}. Correction is required. See MPEP § 608.01(b).

8. The disclosure is objected to because of the following informality: SEQ ID NO is required for TAT-PASS peptide throughout pages 13-15. Appropriate action is required.

9. Claims 6 and 13 are objected to because the claims fail to comply with the requirements of 37 CFR 1.821(d) which required SEQ ID NO.

10. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: it is noted that peptides "FTLEISR" and "LTLKLSR" recited in the original claim 13 have no support in the specification, and the sequence listing in paper and computer readable forms. It is suggested that applicant amend the specification to provide support for said peptides. Please see enclosed notice to comply.

11. Claim 12 is objected to because the recitation of "hsc 73" has no support in the specification as filed. It is suggested that applicant amend the specification to provide support for hsc 73.

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 1-12, and 17-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a method for minimizing the aggregation tendencies of human kappa-4 immunoglobulin light chain (LC) in vitro, the method comprising: (a) identifying the mutation in the amino acid sequence of said protein such as LEN and SMA, (b) substituting each SMA mutation into LEN to identify the residues of a peptide that contribute to fibril formation, (c) synthesizing peptides spanning most of the Variable region of the LC that interacts with a endoplasmic reticulum chaperone selected from the group consisting of BiP and Hsp 70, (d) determining the V_L-derived peptides for their ability to prevent SMA fibril formation in vitro wherein the peptides is selected from the group consisting of TDFTLTI (SEQ ID NO: 5), FTLTISS (SEQ ID NO: 1), FTLKISR (SEEQ ID NO: 6), FTLEISR and LTLKLSR, (2) a method for minimizing the aggregation tendencies of human kappa-4 immunoglobulin light chain (LC) in a cell, the method comprising: (a) identifying the mutation in the amino acid sequence of said protein such as LEN and SMA, (b) substituting each SMA mutation into LEN to identify the residues of a peptide that contribute to fibril aggregation, (c) synthesizing peptides spanning most of the Variable region of the LC that interacts with a endoplasmic reticulum chaperone selected

from the group consisting of BiP and Hsp 70, (d) expressing SMA or LEN in COS cells, (e) treating said cells with said peptides selected from the group consisting of TDFTLTI (SEQ ID NO: 5), FTLTISS (SEQ ID NO: 1), FTLKISR (SEEQ ID NO: 6), FTLEISR and LTLKLSR and (f) determining the V_L-derived peptides for their ability to prevent SMA fibril aggregation in said cell by western blotting or immunoflourosence, **does not** reasonably provide enablement for a method for minimizing the aggregation tendencies of (1) *any* amyloid forming protein the method comprising: a) identifying any first amino acid sequence of *any* protein that is replaced by *any* second amino acid sequence during physiological conditions; and b) preventing the replacement by juxtaposing *any* peptide to *any* first amino acid sequence, (2) the said method is conducted in vivo, (3) the said method wherein the protein is *any* human protein selected from the group consisting of human kappa-IV light chain variable domain and any serine protease inhibitors, (4) the said method wherein the peptide "has" *any* amino acid sequence identical to *any* amino acid sequence in *any* region of the light chain variable domain, (5) the said method wherein the peptide is inserted between residue position numbers 60 and 83 of *any* human protein, and *any* serine protease inhibitors, (6) the said method wherein the peptide "has" the amino acid sequence Phe_{71}-Thr_{72}-Leu_{73}-Thr_{74}-Ile_{75}-Ser_{76}-Ser_{77} and wherein the subscripts denote the positions of the amino acids in domain of human kappa-IV light chain variable domain or in *any* domain of *any* serine protease inhibitors, (7) the said method wherein *any* peptide is inserted when *any* of the protein is partially unfolded, (8) the said method wherein the protein is identical in composition to *any* portion of *any* protein that anchors a hairpin-shaped amino acid sequence to *any* protein, (9) the said method wherein the protein is a greek key fold protein selected from the group consisting of antibody constant domains, transthyretin, beta-2-microglobulin, *any* serine protease inhibitors and crystalline, (10) the said method wherein *any* peptide is inserted at a hairpin anchorage point in the greek key fold protein, (11) the said method wherein *any* peptide is a target for endoplasmic reticulum chaperone, (12) the said method wherein *any* protein is an endoplasmic reticulum chaperone selected from the group consisting of hsp 70, hsc 73 and BiP, (13) the said method wherein *any* peptide interacts with endoplasmic reticulum chaperone, the peptide selected from the group consisting of TDFTLTI, FTLTISS, FTLKISR, FTLEISR, and LTLKLSR, (14) a method for preventing amyloid formation in human kappa-IV light chain variable domain, the method comprising inserting the Phe_{71}-Thr_{72}-Leu_{73}-Thr_{74}-Ile_{75}-Ser_{76}-Ser_{77} into the domain wherein the subscript numbers indicate the residue location on the domain, (15) the said method wherein the domain is partially unfolded at the time of insertion, (16) a method for preventing

fibril assembly, the method comprising a) identifying a region of *any* first aggregating protein moiety that normally interacts with *any* second protein moiety to form the assembly and b) juxtaposing *any* binding protein to said first moiety, (17) the said method wherein the first and second aggregating proteins are *any* immunoglobulin light chains, (18) the said method wherein the binding protein hybridizes with *any* region, and wherein the binding protein is *any* amino acid sequence that is complementary to *any* amino acid sequence of any region for minimizing aggregation of immunoglobulin light chain. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only for a method of minimizing the aggregation tendencies of human kappa-4 immunoglobulin light chain (LC) in *vitro* by identifying the mutation in the amino acid sequence of said protein such as LEN and SMA, substituting each SMA mutation into LEN to identify the residues of a peptide that contribute to fibril formation, synthesizing peptides selected from the group consisting of spanning most of the Variable region of the LC that interacts with a endoplasmic reticulum chaperone selected from the group consisting of BiP and Hsp 70, and determining the V_L-derived peptides selected from the group consisting of TDFTLTI (SEQ ID NO: 5), FTLTISS (SEQ ID NO: 1), FTLKISR (SEEQ ID NO: 6), FTLEISR and LTLKLSR for their ability to prevent SMA fibril formation *in vitro*. The specification further discloses a method for minimizing the aggregation tendencies of human kappa-4 immunoglobulin light chain (LC) in a cell, the method comprises identifying the mutation in the amino acid sequence of said protein such as LEN and SMA, substituting each SMA mutation into LEN to identify the residues of a peptide that contribute to fibril aggregation, synthesizing peptides spanning most of the Variable region of the LC that interacts with a endoplasmic reticulum chaperone selected from the group consisting of BiP and Hsp 70, expressing SMA or LEN in

COS cells, treating said cells with said peptides selected from the group consisting of TDFTLTI (SEQ ID NO: 5), FTLTISS (SEQ ID NO: 1), FTLKISR (SEEQ ID NO: 6), FTLEISR and LTLKLSR and determining the V_L-derived peptides for their ability to prevent SMA fibril aggregation in said cell by western blotting or immunoflourosence.

Other than the specific methods for minimizing the aggregation of the specific amyloid forming protein mentioned above, the specification fails to provide any guidance as how to make and use *any* first and second amino acid sequence of *any* protein and preventing the replacement by juxtaposing *any* peptide to *any* first amino acid sequence because there is no structure associated with any first and second amino acid sequences. Further, there is insufficient guidance and working examples as to what type of amino acid acids within the first or second amino acid sequence must be replace and how it is done in vivo. Finally, claim 1 as written, it is not clear what is preventing the replacement of what by juxtaposing a peptide, in which the structure is unknown, to the first amino acid sequence of *any* amyloid forming protein.

Stevens *et al* teach that amyloid is a generic term for the primarily extracellular accumulation of fibrillar protein deposits and there are at least 20 unrelated, normally non-fibrillar proteins are known precursors of amyloid and each is associated with a specific disease (See page 443, in particular). Stevens *et al* further teach that in contrast to other proteins typically associated with amyloidosis, not all patients who overproduce light chains during myeloma experience development of clinically significant deposit, and no examples of light chains that differ at only a single amino acid position have been found today. Given the diversity of antibody light chains, a virtually unlimited number of variations, both inherited and acquired through somatic mutation can account fibril formation (See page 445, column 2, last paragraph, page 446, in particular). As such, it is unpredictable which undisclosed first and second amino acid sequences and which amino acid substitutions within said sequences would be useful as a method for minimizing the aggregation tendencies of *any* amyloid forming protein in vitro, especially given the indefinite number of the first and second amino acid sequences in relation to the number of unrelated fibrillar proteins. Since the method for minimizing the aggregation of *any* amyloid forming protein in vitro is not enable, it follows that the method conducted in vivo is not enabled. Even if the method is for minimizing the aggregation of human kappa-IV light chain variable domain, there is insufficient guidance as to the structure of any first and second amino acid sequences, in addition to which amino acid within the human kappa-IV light chain variable domain can be substitute.

With regard to claim 3 which recited the method wherein the protein is any serine protease inhibitors, the specification does not teach a method for minimizing the aggregation tendencies of *any* amyloid forming protein by identifying the amino acid sequence of *any* serine protease inhibitors and replacing them with *any* second amino acid sequence as a method for minimizing the aggregation of any amyloid forming protein. Further, there is no working example demonstrating replacing any second amino acid sequence of any serine protease inhibitor could minimizing the aggregation tendencies of any amyloid forming protein. On the contrary, Schubert *et al* teach serine protease inhibitor inhibit amyloid peptide aggregation (See abstract, page 772, second column, second full paragraph, in particular). Gardner *et al* teach immunoglobulin light chain degradation is mediated by a serine protease (See abstract, in particular).

With regard to claim 4, which recited the peptide "has" an amino acid sequence identical to an amino acid sequences in *any* region of the light chain variable domain, the term "has" is opened ended. It expands the peptide to include additional amino acid residues at either or both ends. Given the indefinite number of amino acid can be added to the peptide, there is insufficient guidance and working example as to what type and number of amino acids can be added, in turn, the resulting peptide would be useful for a method of minimizing the aggregation tendencies of *any* amyloid forming protein. It is unpredictable which undisclosed peptide after insertion would be useful for a method of minimizing the aggregation tendencies of any amyloid forming protein, even the peptide can be inserted between residue position numbers of 60 and 83 of either human kappa-IV light chain variable domain or any serine protease inhibitors.

With regard to claim 6, again the term "has" is opened ended. It expands the peptide to include additional amino acid residues at either or both ends in addition to the amino acid sequence Phe_{71}-Thr_{72}-Leu_{73}-Thr_{74}-Ile_{75}-Ser_{76}-Ser_{77}. Given the indefinite number of undisclosed amino acid can be added to the peptide, there is insufficient guidance and working example as to what type and number of amino acids can be added, in turn, the resulting peptide would be useful for a method of minimizing the aggregation tendencies of *any* amyloid forming protein when said protein is partially unfolded. Since the structure of the peptide is unknown and the method of using said peptide for a method of minimizing the aggregation tendencies of any amyloid forming protein is not enable, it follows that any peptide identical in composition to any portion of any protein that anchors a hairpin-shaped amino acids sequence to any protein is not enable.

With regard to claim 10 wherein the protein is any greek key protein such as antibody constant domains, transthyretin, beta-2-microglobulin, serine protease inhibitors, and crystalline, the specification discloses only one specific greek key protein such as human kappa-4 immunoglobulin light chain (LC) for a method of minimizing the aggregation tendencies of human kappa-4 immunoglobulin light chain (LC). The specification does not teach how to make and use any greek key protein for a method of minimizing the aggregation tendencies of *any* amyloid forming protein mentioned above whether it is in vitro or vivo. There is insufficient guidance and working example demonstrating that amino acid substitution in a specific region of human kappa-4 immunoglobulin light chain (LC) is useful as a method for minimizing protein aggregation in any greek key protein such as antibody constant domains, transthyretin, beta-2-microglobulin, serine protease inhibitors, and crystalline. Even using peptides derived from human kappa-4 immunoglobulin light chain (LC) such as TDFTLTI (SEQ ID NO: 5), FTLTISS (SEQ ID NO: 1), FTLKISR (SEEQ ID NO: 6), FTLEISR and LTLKLSR, it is unpredictable whether any of said would interact with just any endoplasmic reticulum chaperone such as hsc 73, in turn, would be useful as a method of minimizing any protein aggregation in any greek key protein such as antibody constant domains, transthyretin, beta-2-microglobulin, serine protease inhibitors, and crystalline.

With regard to claim 12, the specification does not teach the peptide derived from human kappa-4 immunoglobulin light chain (LC) interacts with endoplasmic reticulum chaperone hsc 73. There is no guidance and working example that peptides derived from human kappa-4 immunoglobulin light chain (LC) such as TDFTLTI (SEQ ID NO: 5), FTLTISS (SEQ ID NO: 1), FTLKISR (SEEQ ID NO: 6), FTLEISR and LTLKLSR even interacts with hsc 73.

With regard to claims 19 and 20, the specification does not teach how to make and used any binding protein "hybridizes" with a region of any first aggregating protein moiety that normally interacts with any second protein moiety to form the assembly and juxtaposing any binding protein to said first moiety wherein the binding protein is an amino acid sequence that is "complementary to the amino acid sequence" of the region. The state of the art teaches that only nucleic acid hybridizes to the complement of a nucleic acid encoding the protein. Given the lack of guidance and working example with respect to binding protein "hybridizes" with region and the binding protein is any amino acid that is "complementary to the amino acid sequence", it would take an undue amount of experimentation for even one skilled in the art to practice the claimed invention. In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the

decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

14. Claims 1-12, and 17-20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of *any* (1) amyloid forming protein the method comprising: a) identifying any first amino acid sequence of *any* protein that is replaced by *any* second amino acid sequence during physiological conditions; and b) preventing the replacement by juxtaposing *any* peptide to *any* first amino acid sequence, (2) the said method is conducted in vivo, (3) the said method wherein the protein is *any* human protein selected from the group consisting of human kappa-IV light chain variable domain and any serine protease inhibitors, (4) the said method wherein the peptide "has" *any* amino acid sequence identical to *any* amino acid sequence in *any* region of the light chain variable domain, (5) the said method wherein the peptide is inserted between residue position numbers 60 and 83 of *any* human protein, and *any* serine protease inhibitors, (6) the said method wherein the peptide "has" the amino acid sequence Phe_{71}-Thr_{72}-Leu_{73}-Thr_{74}-Ile_{75}-Ser_{76}-Ser_{77} and wherein the subscripts denote the positions of the amino acids in domain of human kappa-IV light chain variable domain or in *any* domain of *any* serine protease inhibitors, (7) the said method wherein *any* peptide is inserted when *any* of the protein is partially unfolded, (8) the said method wherein the protein is identical in composition to *any* portion of *any* protein that anchors a hairpin-shaped amino acid sequence to *any* protein, (9) the said method wherein the protein is a Greek key fold protein selected from the group consisting of antibody constant domains, transthyretin, beta-2-microglobulin, *any* serine protease inhibitors and crystalline, (10) the said method wherein *any* peptide is inserted at a hairpin anchorage point in the Greek key fold protein, (11) the said method wherein *any* peptide is a target for endoplasmic reticulum chaperone, (12) the said method wherein *any* protein is an endoplasmic reticulum chaperone selected from the group consisting of hsp 70, hsc 73 and BiP, (13) the said method wherein *any* peptide interacts with endoplasmic

reticulum chaperone, the peptide selected from the group consisting of TDFTLTI, FTLTISS, FTLKISR, FTLEISR, and LTLKLSR, (14) a method for preventing amyloid formation in human kappa-IV light chain variable domain, the method comprising inserting the Phe_{71}-Thr_{72}-Leu_{73}-Thr_{74}-Ile_{75}-Ser_{76}-Ser_{77} into the domain wherein the subscript numbers indicate the residue location on the domain, (15) the said method wherein the domain is partially unfolded at the time of insertion, (16) a method for preventing fibril assembly, the method comprising a) identifying a region of any first aggregating protein moiety that normally interacts with any second protein moiety to form the assembly and b) juxtaposing any binding protein to said first moiety, (17) the said method wherein the first and second aggregating proteins are any immunoglobulin light chains, (18) the said method wherein the binding protein hybridizes with any region, and wherein the binding protein is any amino acid sequence that is complementary to any amino acid sequence of any region for minimizing aggregation of immunoglobulin light chain.

The specification discloses only for a method of minimizing the aggregation tendencies of human kappa-4 immunoglobulin light chain (LC) in *vitro* by identifying the mutation in the amino acid sequence of said protein such as LEN and SMA, substituting each SMA mutation into LEN to identify the residues of a peptide that contribute to fibril formation, synthesizing peptides selected from the group consisting of spanning most of the Variable region of the LC that interacts with a endoplasmic reticulum chaperone selected from the group consisting of BiP and Hsp 70, and determining the V_L-derived peptides selected from the group consisting of TDFTLTI (SEQ ID NO: 5), FTLTISS (SEQ ID NO: 1), FTLKISR (SEEQ ID NO: 6), FTLEISR and LTLKLSR for their ability to prevent SMA fibril formation *in vitro*. The specification further discloses a method for minimizing the aggregation tendencies of human kappa-4 immunoglobulin light chain (LC) in a cell, the method comprises identifying the mutation in the amino acid sequence of said protein such as LEN and SMA, substituting each SMA mutation into LEN to identify the residues of a peptide that contribute to fibril aggregation, synthesizing peptides spanning most of the Variable region of the LC that interacts with a endoplasmic reticulum chaperone selected from the group consisting of BiP and Hsp 70, expressing SMA or LEN in COS cells, treating said cells with said peptides selected from the group consisting of TDFTLTI (SEQ ID NO: 5), FTLTISS (SEQ ID NO: 1), FTLKISR (SEEQ ID NO: 6), FTLEISR and LTLKLSR and determining the V_L-derived peptides for their ability to prevent SMA fibril aggregation in said cell by western blotting or immunoflouresence.

With the exception of the specific methods for minimizing the aggregation of the specific amyloid forming protein such as human kappa-4 immunoglobulin light chain (LC) using the specific peptides derived from human kappa-4 immunoglobulin light chain (LC) mentioned above, there is insufficient written description about the structure associated with functions of *any* (1) amyloid forming protein, (2) *any* first and second amino acid sequences, (3) *any* serine protease inhibitors, (4) *any* peptide "has" an amino acid sequence identical to any amino acid sequence in any region of the light chain variable domain, (5) *any* peptide "has" the amino acid sequence the amino acid sequence Phe_{71}-Thr_{72}-Leu_{73}-Thr_{74}-Ile_{75}-Ser_{76}-Ser_{77}, (6) *any* peptide is inserted when the protein is partially unfolded, (7) *any* peptide is identical to *any* portion of *any* protein that anchors a hairpin-shaped amino acid sequence to the protein, (8) *any* peptide is inserted at a hairpin anchorage point in the greek key fold protein, (9) *any* peptide is a target for an endoplasmic reticulum chaperone, (10) *any* region of a first aggregating protein moiety that interacts with any second protein moiety and juxtaposing any binding protein to said first moiety. Further, the term "has" or "comprising" is opened ended. It expands the peptide to include additional amino acid residues at either or both ends. Given the indefinite number of amino acids could be added to the peptide, there is insufficient structure associated with functions of said peptides. With regard to *any* amyloid forming protein, the specification discloses only one amyloid forming protein, that is, human kappa-4 immunoglobulin light chain (LC) and only five human kappa-4 immunoglobulin light chain (LC) derived peptides such as the ones recited in claim 13 for a method of minimizing the aggregation of only human kappa-4 immunoglobulin light chain (LC). Given the lack of a written description of *any* additional representative species of amyloid forming protein and peptides, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

15. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

16. Claims 1-13, and 17-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "protein" in claim 1 line 3 is indefinite and ambiguous because it is not clear the amino acid of which protein, the amyloid binding protein or the endoplasmic reticulum chaperon protein, is identified.

The recitation of "preventing the replacement" in claim 1, line 5 is incomplete and indefinite. One of ordinary skill in the art cannot appraise the metes and bounds of the claimed invention.

The recitation of "protein" in claim 5, line 2, which depends on claim 3, is ambiguous and indefinite. The specification discloses the peptide is inserted between residue position numbers 60 and 83 of human kappa IV light chain only and not serine protease inhibitors.

The recitation of "protein" in claim 7 is indefinite and ambiguous because it is not clear which protein, the amyloid binding protein or the endoplasmic reticulum chaperon protein, is partially unfolded.

The recitation of "protein moiety" in claim 17 is ambiguous and indefinite because the specification does not define the term "protein moiety".

The recitation of "protein hybridizes" in claim 19 is ambiguous and indefinite because protein does not "hybridizes", only nucleic acid sequence "hybridizes".

The recitation of "an amino acid sequence that is complementary to the amino acid sequence of the region" in claim 20 is indefinite and ambiguous. An amino acid sequence does not complement to any amino acid sequence. Only nucleic acid binds to its complement. Appropriated correction is required.

17. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

A DOCPHOENIX

BACKFILE DOCUMENT INDEX SHEET

APPL PARTS

_____ IMIS ____
Internal Misc. Paper

_____ LET. ____
Misc. Incoming Letter

_____ 371P ____
PCT Papers in a 371Application

_____ A... ____
Amendment Including Elections

_____ ABST ____
Abstract

_____ ADS ____
Application Data Sheet

_____ AF/D ____
Affidavit or Exhibit Received

_____ APPENDIX ____
Appendix

_____ ARTIFACT ____
Artifact

_____ BIB ____
Bib Data Sheet

_____ CLM ____
Claim

_____ COMPUTER ____
Computer Program Listing

_____ CRFL____
All CRF Papers for Backfile

_____ DIST ____
Terminal Disclaimer Filed

_____ DRW ____
Drawings

_____ FOR ____
Foreign Reference

_____ FRPR ____
Foreign Priority Papers

_____ IDS ____
IDS Including 1449

_____ NPL ____
Non-Patent Literature

_____ OATH ____
Oath or Declaration

_____ PET. ____
Petition

_____ RETMAIL____
Mail Returned by USPS

_____ SEQLIST ____
Sequence Listing

_____ SPEC ____
Specification

_____ SPEC NO ____
Specification Not in English

_____ TRNA ____
Transmittal New Application

OUTGOING

_____ CTMS ____
Misc. Office Action

_____ 1449 ____
Signed 1449

_____ 892 ____
892

_____ ABN ____
Abandonment

_____ APDEC ____
Board of Appeals Decision

_____ APEA ____
Examiner Answer

_____ CTAV ____
Count Advisory Action

_____ CTEQ ____
Count Ex parte Quayle

_____ CTFR ____
Count Final Rejection

_____ CTNF ____
Count Non-Final

_____ CTRS ____
Count Restriction

_____ EXIN ____
Examiner Interview

_____ M903 ____
DO/EO Acceptance

_____ M905 ____
DO/EO Missing Requirement

_____ NFDR ____
Formal Drawing Required

_____ NOA ____
Notice of Allowance

_____ PETDEC____
Petition Decision

INCOMING

_____ AP.B ____
Appeal Brief

_____ C.AD ____
Change of Address

_____ N/AP ____
Notice of Appeal

_____ PA.. ____
Change in Power of Attorney

_____ REM ____
Applicant Remarks in Amendment

_____ XT/ ____
Extension of Time filed separate

Internal

_____ SRNT____
Examiner Search Notes

_____ CLMPTO ____
PTO Prepared Complete Claim Set

_____ WCLM ____
Claim Worksheet

_____ WFEE ____
Fee Worksheet

File Wrapper

_____ FWCLM ____
File Wrapper Claim

_____ IIFW ____
File Wrapper Issue Information

_____ SRFW ____
File Wrapper Search Info

18. Claims 1-8, 10-13 and 15-20 are rejected under 35 U.S.C. 102(a) as being anticipated by Davids *et al* (J Immunology 163: 3842-50, Oct 1999; PTO 892).

Davids *et al* teach a method for minimizing or preventing the aggregation or fibril assembly of an amyloid forming protein such as human immunoglobulin light chain variable domain (See entire document, in particular). The reference method involves identifying the mutation in the amino acid sequence of the human immunoglobulin kappa IV light chain variable domain such as LEN k chain and SMA and REC kappa chain and test their ability to bind to binding protein such as BiP under physiological conditions (See page 3844, binding of V_L domains of LC to BiP, page 3845, Identifying Potential BiP binding sites in V_L, in particular), replacing the amino acid residues that contact the bound peptide in BiP, testing the peptides derived from human immunoglobulin light chain variable domain for their ability to compete with the binding of the labeled peptide such as TDFTLTI and FTLTISS to BiP (See page 3847, column 1, last paragraph, in particular). Davids *et al* teach the reference method can be conducted in vivo by expressing the human immunoglobulin kappa light chain variable domain such as LEN k chain, SMA, or REC kappa chain in COS cell. The reference peptides such as TDFTLTI and FTLTISS have amino acid sequences identical to an amino acid sequence in a region such as 69-75 and 71-77, respectively, of the light chain variable domain (See Table 1, in particular). The reference method wherein the peptide binds between residue position number 60 and 83 of the protein such as the human immunoglobulin light chain variable domain (See Table 1, in particular). The reference method wherein the peptide is 100% identical to the claimed sequence Phe_{71}-Thr_{72}-Leu_{73}-Thr_{74}-Ile_{75}-Ser_{76}-Ser_{77}, wherein the subscripts inherently denoted the positions of the amino acids in the variable domain of the reference human immunoglobulin kappa light chain variable domain (See page 3847, column 1, in particular). The reference method wherein the peptide inherently binds to the human immunoglobulin kappa light chain variable domain when it is partially unfolded in the endoplasmic reticulum as long as they have not completed their disulfide bonding (See page 3848, column 2, last paragraph, in particular). The reference method wherein the peptide is identical in composition to a portion of a protein such as V_L that anchors a hairpin-shape amino acids to the protein and the reference peptide such as TDFTLTI and FTLTISS is inserted at a hairpin anchorage point in the greek key fold protein (See Fig 4, in particular). The reference method wherein the peptide such as TDFTLTI and FTLTISS interact with endoplasmic reticulum chaperone such as hsp70 and BiP (See page 3842, column 1, Fig 3, in particular). The reference method also prevent fibril assembly such as

identifying the region of the human immunoglobulin kappa light chain variable domain (fist aggregating protein) that normally interacts with a binding protein such as the BiP and juxtaposing the reference binding protein by exposing the BiP protein to the human immunoglobulin kappa light chain variable domain (first aggregating protein) in the present of the reference peptides such as TDFTLTI and FTLTISS derived from immunoglobulin light chains (second protein moiety) where the reference BiP binding protein binds to a region within the immunoglobulin light chains (See page 3844, binding of V_L domains of LC to BiP, page 3845, Identifying Potential BiP binding sites in V_L, See Table 1, in particular). Thus, the reference teachings anticipate the claimed invention.

19. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Boland *et al* (J Biol Chem 271(30): 18032-44, 1996; PTO 892).

Boland *et al* teach a method of minimizing the aggregation of an amyloid forming protein such as amyloid-β peptide. The reference method comprises identifying amino acid sequence of the amyloid-β peptide using a series of deletion, substitution and chimeric amβ/a1-AT peptides and preventing the biding of the reference peptides to the serpin-enzyne complex receptor (See abstract, Figs 6 and 7, page 18034, column 2, Correlation among SEC-R binding, Toxicity, and Aggregation of amyloid-β peptide, in particular).

20. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

21. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was

made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

22. Claims 1, 3 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davids *et al* (J Immunology 163: 3842-50, Oct 1999; PTO 892) or Boland *et al* (J Biol Chem 271(30): 18032-44, 1996; PTO 892) each in view of Gardner *et al* (J Biol Chem 268(34): 25940-47, 1993; PTO 892), Schubert *et al* (European J Neuroscience 9: 770-777, 1997; PTO 892) or Ohashi *et al* (Virchows Arch 428(1): 37-46, 1996; PTO 892).

The teachings of Davids *et al* and Boland *et al* have been discussed supra.

The claimed invention as recited in claims 3 and 9 differs from the references only by the recitation that the protein is serine protease inhibitor.

The claimed invention as recited in claim 9 differs from the references only by the recitation that the protein is beta-2-microglobulin.

Gardner *et al* teach a serine protease inhibitor such as 3,4-DCI that protects newly synthesized immunoglobulin light chain from degradation (See page 25944, column 2, k Chain Degradation Is Inhibited by Serine Protease Inhibitors, Fig 8, in particular).

Schubert *et al* teach a serine protease inhibitor such as Serpins that inhibits amyloid peptides aggregation and toxicity (See entire document, page 771, column 2, Serpins inhibits amyloid and amylin toxicity and aggregation, in particular).

Ohashi *et al* teach beta-2-microglobulin amyloidosis associated with long-term heamodialysis which has an increased in matrix metalloproteinases such as MMP-1, while AL amyloidosis is involved in immunoglobulin light chain deposits in the particular tissues (See abstract, page 44, column 2, in particular). Ohashi *et al* teach serine proteinases have been implicated in the degradation of extracellular matrix components and various proteinase inhibitors are useful for inhibiting joint destruction (See page 37, column 2, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to inhibit serine proteinase using proteinase inhibitor such as 3,4-DCI as taught by Gardner *et al* or the Serpins as taught by Schubert *et al* for a method of minimizing the aggregation any amyloid forming protein such as immunoglobulin light chain as taught by Davids et al or the beta amyloid peptide as taught by Boland *et al* or the beta-2-microglobulin as taught by Ohashi *et al*. From the combined teachings of the references, it is apparent that one of

ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because Gardner *et al* teach serine protease inhibitor such as 3,4-DCI can protect newly synthesized immunoglobulin light chain from degradation (See page 25944, column 2, k Chain Degradation Is Inhibited by Serine Protease Inhibitors, Fig 8, in particular). Schubert *et al* teach serine protease inhibitor such as Serpins can inhibit amyloid peptides aggregation and toxicity (See entire document, page 771, column 2, Serpins inhibits amyloid and amylin toxicity and aggregation, in particular). Ohashi *et al* teach serine proteinases have been implicated in the degradation of extracellular matrix components and various proteinase inhibitors are useful for inhibiting joint destruction and beta-2-microglobulin amyloidosis associated with long-term heamodialysis that has an increased in matrix metalloproteinases such as MMP-1 (See page 37, column 2, in particular).

23. Claims 1 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davids *et al* (J Immunology 163: 3842-50, Oct 1999; PTO 892) or Boland *et al* (J Biol Chem 271(30): 18032-44, 1996; PTO 892) each in view of US Pat No. 5,276,059 (Jan 1994; PTO 892).

The teachings of Davids *et al* and Boland *et al* have been discussed supra.

The claimed invention as recited in claim 9 differs from the references only by the recitation that the protein is selected from the group consisting of antibody constant domains and transthyretin.

The '059 patent teaches protein such as transthyretin is involved with Familial amyloid polyneuropathy, beta-2-microglobulin is involved with amyloidosis or fibril aggregation associated chronic dialysis, immunoglobulin constant domain (IgG 1 (γ1) is involved with macroglobulin or idiopathic (primary) myeloma (See Table 1, column 5, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the immunoglobulin light chain as taught by Davids *et al* or the amyloid beta peptide as taught by Boland *et al* for the beta-2-microglobulin or immunoglobulin constant domain or the transthyretin as taught by the '059 patent for a method of minimizing the aggregation tendencies of any amyloid forming protein. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the '059 patent teaches any protein such as beta-2-microglobulin or immunoglobulin constant domain or the transthyretin can form amyloid deposits and inhibition of amyloid deposit is beneficial in the treatment and prevention of these diseases (See column 5, lines 5-7, in particular).

24. No claim is allowed.

25. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

26. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Phuong N. Huynh, Ph.D.
Patent Examiner
Technology Center 1600
July 29, 2002

Christina Chan

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600